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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,184	02/12/2001	Howard Sands	12636-898	6040

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,184	SANDS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request of Continued Examination and the Amendments filed on January 14, 2004 is acknowledged. Claims 1-4 and 6-36 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-18, and 20-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "pharmacologically acceptable lipophilic liquid vehicle with at least one membrane-forming lipid" and an outer layer comprising phospholipids does not have support in the specification as originally filed. The originally filed specification only has support for a water-insoluble acceptable lipophilic liquid with camptothecin and an outer layer comprising at least one membrane-forming lipid. However, applicant is now claiming a lipophilic liquid, camptothecin, at least one membrane-forming lipid, and an outer layer made of phospholipids. Applicant does not have support for membrane forming lipid inside the microdroplet and in the outside layer composition. A review of the specification shows that applicant has only support for the membrane-forming lipid in the outer layer and not in the internal compartment of the microdroplet, which would

form a double layer. If applicant does contend there is support for the amendment, it is requested that the applicant clearly identify the page and lines in the specification that lends support to applicant's amended microdroplet structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 6-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haynes (4725442) in view of Burke (5552156).

Haynes discloses microdroplets (200 angstroms up to a micron) of water insoluble drugs containing a water-insoluble pharmaceutically acceptable liquid surrounded by a layer of phospholipids, which are suitable for injection (Note the abstract, columns 2-8, and claims). Haynes discloses phospholipids, cholesterol, etc are utilized as the membrane-forming lipid and a mixture of lipids may be used to vary the surface properties and reactivity of the microdroplet (col. 5 and 6, line 56 to line 50). Although Haynes discloses his invention using anesthetics in examples, according to the reference, the composition can be used to deliver any water insoluble/oil soluble drug via injection (col. 1, lines 26-39). The reference teaches the use of alkanes, fluorocarbons, natural plant derived oil, etc. for the organic phase. See column 5, lines 9-55. Haynes further teaches anti-cancer agents as the drugs which can be practiced in his invention (note col. 8, lines 27-28 and claim 15).

Hayes does not specifically teach camptothecin as the anti-cancer drug or instant pH.

Burke teaches camptothecin drugs encapsulated by lipids to overcome the insolubility and instability problems of camptothecin for intravenous administration. Burke states that camptothecin drugs bind the lipid bilayer of liposomes with great affinity and intercalates between the acyl chains of the lipid. Thus, the lactone ring of the camptothecin membrane bound drug is removed from the aqueous environment inside and outside of the liposome and is protected from hydrolysis, preserving the activity of the drug. Further, Burke teaches reducing the internal pH of the liposome to prevent hydrolysis of certain camptothecin drugs. See column 3, line 59 to column 4, line 2. Thus, the lipid encapsulation creates an internal environment with a low pH to prevent hydrolysis of camptothecin drugs. (Note abstract)

WO 99/61001 discloses suspensions of submicron and micron sized particles of water insoluble biologically active substances such as antineoplastic agents containing lipoid and surface modifiers, phospholipids. WO states that sterilization of injectable suspensions is necessary for their parenteral administration. See page 1. However, sterilization causes heat induced coagulation, flocculation, and particle growth and thermoprotecting agents reduce this. Sugars such as trehalose and mannitol are taught as the thermoprotecting agents and should be included for protection during sterilization (note the abstract, examples and claims). The reference also teaches the use of Lipoid E80 (Table 1). WO teaches that the formulation may contain suitable amount of buffering salts and pH adjusting agents since it is known to those skilled in the art of

phospholipids that a pH lower than 5 and higher than 9, the phospholipids molecules undergo extensive hydrolysis. Therefore, the pH of the suspension was usually adjusted to within this range prior to homogenization. See page 15.

It is deemed obvious to one of ordinary skill in the art to use any hydrophobic drug including camptothecin, known in the art as a hydrophobic anticancer drug, with a reasonable expectation of success since Haynes provides the general guidance to prepare the compositions. One would be motivated to do so since Haynes suggests the incorporation of anticancer drugs into the formulation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate Burke' s camptothecin in Haynes's phospholipid layers and utilize the instant pH. One would be motivated to do so since Burke teaches the advantages of encapsulating camptothecin, a water-insoluble drug, in phospholipid structures to successfully deliver instant cancer drugs by overcoming instability and insolubility problems caused by hydrolysis by the aqueous phase. Therefore, one would be motivated to utilize the instant pH of both the internal liposome's aqueous phase and the external phase to prevent hydrolysis of camptothecin's lactone ring.

Furthermore, WO teaches that the manipulation of the pH of the aqueous phase when working with phospholipids, is known to skilled artisan, to prevent hydrolysis. Therefore, it is deemed obvious to a skilled artisan to manipulate the pH through routine optimization using conventional knowledge of phospholipid technology.

Lastly, one would further look to WO 99/61001 and include sugars such as trehalose or mannitol in the compositions of Haynes. One would be motivated to do so

since WO teaches that the instant sugars are thermoprotectants and protect the phospholipid particle suspensions during sterilization to prevent heat induced coagulation, flocculation, or particle growth.

Response to Arguments

Applicant argues that Haynes does not disclose camptothecin or the instant pH limitations to minimize the hydrolysis of the alpha-hydroxy rings of the drug. Applicant argues that although Burke teaches reduced pH to prevent hydrolysis of the camptothecin drugs, Burke's teachings pertain to the internal environment of liposomes or micelle structures and not the external phase.

Applicant's arguments have been fully considered but they are not persuasive. Firstly, the examiner points out the rejections are made under obviousness and therefore the primary reference need not teach all the limitations of the instant invention, it merely needs to suggest it. Haynes teaches microdroplets of water-insoluble drugs such as anti-cancer agents, coated with phospholipids. The examiner relies on the secondary reference to teach the specific anti-cancer drug, camptothecin. Burke teaches the encapsulation of camptothecin to protect the function and activity of the drug and prevent hydrolysis. Although Burke speaks to pH reduction mainly in the internal liposome compartment, the prior art clearly recognizes the problem of hydrolysis of camptothecin drugs in aqueous environments both on the *outside* and *inside* of the liposome. See column 3, lines 59-62. Thus, can apply this teaching to reduction of the pH both in and outside the liposome. A patent is not limited to the

preferred embodiments or examples rather it can be relied upon for its broad disclosure. Furthermore, the examiner relies on WO not only for its teachings of the instant sugars but also for its teachings of the conventional phospholipid technology. WO clearly states that it is known that the pH of the suspension affect the phospholipids and a pH of lower than 5 or higher than 9 causes hydrolysis and it is conventional to experiment and manipulate the pH within this range.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-242-0614. The examiner can normally be reached on M-F (8:00-5:00) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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